Attorney Docket No. YALE-025/02US **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Patrick C. Kung, *et al.*	Confirmation No.: 9303
Serial No.: 09/830,033	Group Art Unit: 1631
Filed: October 22, 2001	Examiner: Michael L. Borin

For: PHYTOMICS: A GENOMIC-BASED APPROACH TO HERBAL COMPOSITIONS

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

This Pre-Appeal Brief Request is filed in response to the final Office Action dated July 27, 2009. Pursuant to the requirements set forth in the Official Gazette (July 12, 2005), this Request is filed concurrently with a Notice of Appeal and prior to the filing of an Appeal Brief. Review and reconsideration of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

In the final Office Action dated July 27, 2009, claims 83, 84, and 87 to 89 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Khwaja et al. (U.S. Patent No. 6,113,907) in view of Lockhart et al. (U.S. Patent No. 6,040,138) or Xiong et al. (Molecular Breeding, 1998, vol. 4, 129-136) and Wallace (Molecular Medicine Today, 1997, vol. 3, 384-389), and further in view of Ray et al. (U.S. Patent No. 4,570,380).

Specifically, the Examiner alleges that it would have been obvious to one skilled in the botanical arts at the time of the invention to apply the genomic-based bioassays as described in Lockhart et al. and Wallace, or alternatively Xiong et al. and Wallace, to the quality control method of Khwaja et al. because one skilled in the botanical art was aware of the importance of gene expression in plants for quality control as indicated by Ray et al.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness for at least the reasons discussed below.

I. The Combined Disclosures of the Cited Art Fail to Teach or Suggest All Claim Limitations

Applicants respectfully submit that the cited references, taken alone or in combination, fail to teach or suggest at least the exposing and determining steps as claimed in the present application.

The present quality control method comprises, among other things, the steps of exposing a biosystem, such as cell or tissue, to a whole batch of herbal composition, i.e., the standardized batch or the test batch; and determining a differential gene expression profile of the exposed biosystem as compared to a control, i.e., an unexposed biosystem. The differential gene expression profile is determined by using a genomic-based bioassay method.

The method of the primary reference, i.e., Khwaja et al., involves the steps of separating/isolating a botanical sample into multiple fractions, and measuring the biological activity of each individual fraction against an enzyme or receptor. In contrast, the botanical samples of the present invention, i.e., the standardized and test batches, are each tested as a whole sample without fractionation. Furthermore, Khwaja et al. do not mention or allude to a genomic-based bioassay, let alone the use thereof in a quality control method.

Inasmuch as the Khwaja et al. method markedly differs from the claimed method, the secondary references fail to cure the deficiencies of Khwaja et al.

The Examiner has asserted that the Lockhart method can be used for identifying differential gene expression between two samples. However, the Lockhart method uses two different biosystems, i.e., a pathological biosystem and a healthy biosystem, to obtain differential gene expression. In contrast, the claimed method uses only one biosystem to obtain differential gene expression. Specifically, as recited by independent claim 83, a biosystem is exposed to a standardized batch in step (b)(i) and the same biosystem is also exposed to a test batch in step (c)(i). More importantly, the use of two different biosystems as described by Lockhart et al. contradicts the present invention because the claimed method has to use the same biosystem for both the standarized and the tested batches in order to assure the consistency in comparing the differential gene expressions of the standarized and tested batches.

Xiong et al. focus on the genetics and gene expression profile of the rice plants themselves for plant identification. That is, the differential gene expression in Xiong et al. is that of botanical materials, i.e., rice plants. In contrast, the differential gene expression in the claimed method is that of a biosystem, such as cell or tissue, not that of the botanical materials.

Wallace is a review article discussing the use of genomic-based technology for diagnostics and research in general terms, while Ray et al. disclose a method for hybrid cotton production by utilizing a

cytoplasmic-genetic male sterile system for forming F1 hybrid cottonseeds. Neither Wallace nor Ray et al. disclose or suggest the exposing and determining steps as claimed in the present invention.

Thus, at least the limitations of the exposing and determining steps in the claimed method are not met by the cited references, solely or in combination.

II. There Is No Motivation for Making a Modification in Neither the Cited Art Nor the Common Knowledge

Cited References:

Applicants respectfully submit that there is no disclosure or suggestion available in the cited references which would motivate one skilled in the art to modify the Khwaja method with genomic-based bioassays for assuring the quality of herbal compositions.

First, Ray et al. do not show that one skilled in the botanical art was aware of the importance of gene expression in plants for quality control purposes as alleged by the Examiner. Ray et al. do not even remotely mention genomic-based assays or differential gene expression. Although Ray et al. discuss gene pairs to some extent, such discussion is directed to the correlation between certain gene pairs and the plant leaf configuration and is not related to genomic-based assay or differential gene expression at all, let alone the application of these technologies in quality control of herbal compositions.

Xiong et al. disclose the genetics and gene expression profile of the rice plants themselves for plant identification, but do not teach or suggest the use of genomic-based assay or differential gene expression for the purpose of producing herbal compositions with consistent quality.

Neither Lockhart et al. nor Wallace discloses or contemplates the use of genomic-based technology for controlling the quality of herbal compositions.

As acknowledged by the Examiner, Khwaja et al. do not teach or suggest the use of genomic-based bioassays in a quality control method for producing botanical products.

Thus, none of the cited references provides one skilled in the art with a motivation to apply genomic-based bioassays to a quality control method for herbal compositions.

Common Knowledge:

As stated in the Declaration under 37 C.F.R. §1.132 by Dr. Dan Theodorescu dated March 7, 2005, Dr. Theodorescu (paragraph 6, pages 6 to 7), a person of ordinary skill in the art who was aware of gene expression technology and the need for botanical quality control, did not envision applying

genomic-based assays to botanical quality control in such a particular way to arrive at the claimed method at the priority filing date of the present application.

Impermissible Hindsight:

Due to the lack of a motivation for making modification of the prior art methods in both the cited references and the common knowledge in the art, it logically follows that the Examiner has improperly gleaned from Applicant's own application and exercised the impermissible hindsight to reconstitute a motivation to arrive at this clearly erroneous conclusion of obviousness. In *Graham*, the Supreme Court has cautioned against using hindsight whereby the teachings of the invention are read into the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966). More recently, the Supreme Court recognized in *KSR* that "hindsight bias" and "ex post reasoning" as inappropriate in determination of obviousness. *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1742 (2007).

The Examiner reminds Applicants that "unobviousness cannot be established by attacking the references individually" (Final Office Action, page 6). Applicants have previously argued and herein again reiterate that it is the unobviousness of the combination of the cited "prior art" that has been and continues to be the Examiner's error in applying and maintaining the one remaining rejection. Accordingly, Applicants respectfully submit that on both from a legal and technical basis the alleged combination is improper, and hereby respectfully request the withdrawal of the obviousness rejection.

III. Secondary Considerations Rebutting the Obviousness Rejection

The §103 rejection also fails because there are long felt but unresolved needs and failure of others for the development of a method of controlling the quality of herbal compositions. Specifically, despite the fact that herbal medicines have been used for many centuries in the treatment of various diseases, more advanced development of herbal medicines has been hindered by the unique problem of unpredictable variability of herbal medicines due to the lack of quality control method (page 1, line 10 to page 2, line 7, and page 7, line 22 to page 8, line 6 of the present application; and column 2, line 40 to column 3, line 2 of Khwaja et al.). To resolve this long felt need for a quality control method, a great deal of effort has been directed to the separation and isolation of the biologically active components from botanical materials. But this purification approach diminishes the benefits of complex and synergistic biological activity provided by naturally occurring botanical material (Khwaja et al., column 3, lines 3 to 43). Khwaja et al. attempt to provide a method for producing pharmaceutical grade of St. John's Wort by using compositional and activity fingerprints. However, as discussed above, Khwaja et al. applies fractionation technique to process the samples, i.e., separating

and isolating the samples into multiple fractions. Thus, the Khwaja method does not overcome the disadvantage of the purification approach. As shown by paragraph 5 (pages 2 to 4) of the Declaration under 37 C.F.R. §1.132 by Dr. Dan Theodorescu dated March 7, 2005, others have also failed in their attempts to resolve the problem. For example, despite the promising initial clinical data, the clinical trial of BotanicLab's herbal medicine, namely, PC-SPES, was halted due to quality control problems.

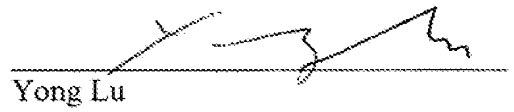
In *Graham v. John Deer Co. of Kansas City*, 383 U.S. 1, 17-18, the United States Supreme Court set out an objective analysis for applying §103 rejections where secondary considerations, such as long felt but unresolved needs and failure of others, are considered as important factors against finding of obviousness. In view of the above-discussed long felt but unresolved needs and failure of others in developing a quality control method for assessing herbal compositions, Applicants respectfully request reconsideration and withdrawal of the present §103 rejection.

Therefore, in view of the failure of the cited art to disclose all claim limitations, the lack of a motivation for making modifications, and the showing of the secondary considerations, the Examiner has not established a *prima facie* case of obviousness.

If the Examiner or the Panel have any questions relating to this Request or to the application in general, they are encouraged to contact the undersigned by telephone so that allowance of the present application may be expedited.

Dated: January 27, 2009

Respectfully submitted,
COOLEY GODWARD KRONISH LLP

By: 

Yong Lu
Reg. No. 56,038

Cooley Godward Kronish LLP
ATTN: Patent Group
777 6th Street, Suite 1100
Washington, DC 20001
Tel: (202) 842-7861 or (703) 456-8000
Fax: (202) 842-7899